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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/697,863	10/27/2000	Stefan M C Pype	4555US	7540

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EXAMINER
LIU, SAMUEL W

ART UNIT	PAPER NUMBER
1653	13

DATE MAILED: 12/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/697,863	PYPE ET AL.	
	Examiner	Art Unit	
	Samuel W Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,11,19-21 and 23-25* is/are pending in the application.

4a) Of the above claim(s) *2-4,7,11,21 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,6,19,20,24 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *PCT/EP99/03025* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I, Claims 1, 3, 5-6, 19 and 20 without traverse filed 4 November 2002 (Paper No. 10) is acknowledged, and addition of new claims 23-25 and cancellation of claims 8-10, 12-18 and 22 are entered.

The response asserts that the limitations for method claims are inappropriate in compound claims (the third paragraph of the response). Note that the restriction requirement is applied to all claims of the current application. For the reason of the record, the requirement as set forth in the previous Office action stands.

Applicants further elect SEQ ID NO:2 and CD40-related diseases for the examination. Therefore, claim 3 and newly added claim 23 are withdrawn from consideration as being drawn to non-elected species SEQ ID NO:4, and claims 1, 5-6, 19 and 20 and new claims 24 and 25 are examined in this Office action.

In addition, although election for Group I does not require to elect a protein interacting compound, the response elects TTRAP as the disclosed protein interacting compound (see lines 11-12 at third paragraph). It should be note that TTRAP *per se* is not such the compound, rather a subject protein, TTRAP, *i.e.*, SEQ ID NO:2 peptide sequence instead; TTRAP is the protein with which the disclosed compound interacts.

Specification/Claim Objections

The disclosure is objected to because of the following informalities:

In page 2, line 12, "TTRAP" should be spelled out in full for the first instance of use. See also page 2, line 17 "TNF"; page 16, line 26, GVHD"; page 17, line 16, "MHC"; and page 25, line 26, "GST-CD40".

In page 4, line 19, "SEQ ID NO.2" should be changed to SEQ ID NO:2. The same changes should be made throughout the specification.

In page 4, line 19, "SEQ.ID.NO.2" should be changed to SEQ ID NO:2.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 1, 5, 6, 19-20 and 24-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite in the recitation " capable of" because it is not clear whether or not binding must invariably occur (see "...TTRAP form a complex with ..." instead). Claim 1 is vague as to "depicted in SEQ ID NO:2" because the recitation is unclear regarding whether or not full-length amino acid sequence of SEQ ID NO:2 is completely disclosed; suggest "amino acid sequence of SEQ ID NO:2" instead. In addition, Claim 1 recites the term "TNF"; the term should be spelled out in full for the first time of recitation in the claim. The dependent claims are also included in the rejection. Further, the comma preceding to the term "including" in the

recitation at line 5 of claim 1 "including the cytoplasmic domain CD40." should be deleted for claim clarity.

Claim 6 is awkward in recitation "...protein claim 1..."; claim appears to recite "...protein of claim 1". See also claim 19.

Claim 19 is unclear as to "one or more isolated functional proteins"; since claim discloses only one isolated protein (SEQ ID NO:2), it is not clear with regard to whether or not the disclosed pharmaceutical composition contains protein(s) other than SEQ ID NO:2 polypeptide, or the said proteins include a functional fragments of SEQ ID NO:2. Also, Claim 19 is indefinite as to "and/or"; which is it, "and" or "or". See also claim 20. In addition, claim 19 contains two periods at the end of the claim. Only one (1) is necessary.

Claim 20 is indefinite in the recitation "the CD40 related pathway" at line 5 of the amended claim because (i) there is insufficient antecedent basis in the claims; does the recited pathway refer to a particular CD40 pathway? (ii) the recitation is unclear as to "CD40 related pathway" wherein "related" renders the recitation interpretation so broad that it becomes indefinite; this is due to a consideration of that the currently discovered cell signaling pathways, *e.g.*, G-protein receptor coupled signaling pathway, tyrosine kinase signaling pathway and steroid hormone receptor signaling pathway *etc.* are *cross-talking one other* to which the CD40 pathway is directly or indirectly related; it appears that the instant invention refers to CD40 *mediated* pathway; (iii) further, the term "pathway" is not apparent as it may refer to a metabolic pathway or a signal transduction pathway. Therefore, suggest "CD40-mediated signaling pathway" instead.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 5-6, 19 and 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for isolating CD40 interacting protein, *i.e.*, TTRAP (TRAF and TNF receptor associated protein) SEQ ID NO:2, identifying TTRAP interactions with TNF (tumor necrosis factor) receptor, TRAF (TNF receptor-associated factor), and CD40 protein, does not reasonably provide enablement for all polypeptide variants having 70-100% homology to or a fragment of SEQ ID NO:2, and a pharmaceutical composition comprising a compound interacting with the polypeptide variants for treating a CD40-related disease. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The specification is insufficient to enable a skilled artisan to practice the invention as broadly claimed without an undue amount of experimentation.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *in re* Wands 8 USPQ2d 1400, 1400 (Fed. Cir. 1998). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but not limited to: 1) the nature of the invention; 2) the breath of the claims; 3) the predictability or unpredictability of the art; 4) the amount of

direction or guidance presented; 5) the presence or absence of working examples; 6) the quantity of experimentation necessary; 7) the relative skill of those skilled in the art.

Each factor is addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

(1) The nature of the invention:

The claims of the current application are directed to numerous variants of polypeptide fragments. Of them, some would be nonfunctional or partially functional, absent the factual evidence to the contrary. The current disclosure provides no working examples with respect to structure and function of these variants nor how to *a priori* determine which one(s) would or would not have been functional or not.

The instant application has provided a description of isolation and identification of the amino acid sequence (SEQ ID NO: 2), TTRAP full-length sequence, and characterizing TTRAP interaction with TNF receptor (TNF-RII), TRAF3 and TRAF 5, and CD40 receptor. The specification does not provides factual evidence that all variant forms of the polypeptide SEQ ID NO:2 and fails to describe the consequence of the variants and their pharmaceutical use in respect to the full length polypeptide and fails to describe the common attributes or characteristics that identify members of the genus that encompasses any members of the variants ranging from up to 20%.

Applicants are not in possession of all the variants for their interaction with TNF receptor, the TRAF proteins and CD40 receptor and for therapeutic activity, *i.e.*, treating CD40-related disease stares comprising any amino acid sequence (***a***) any peptide fragment comprising any amino acid sequence 70% to less than 100% identical to full-length sequence of SEQ ID

NO:2; (***b***) any biologically active fragment having any amino acid sequence of SEQ ID NO: 2; (***c***) any composition comprising any polypeptide of foregoing (***a***) and (***b***). Absent is a pertinent written description of this regard.

There is insufficient guidance as to which amino acid residue within the polypeptide can be deleted, substituted and whether the resulting polypeptide would maintain the same structure as SEQ ID NO:2 protein in aqueous solution. Honig *et al.* teach that the amino acid residues of a protein that can tolerate structural change (*e.g.*, mutations: conservative substitution or no substitution, addition or deletion) which are critical to maintain the protein's structure will require guidance (see *Honig, B.* (1999) *J. Mol. Biol.* 293, 283-293). Given the lack of sufficient guidance and working examples, predicting what changes can be made to the amino acid sequence of SEQ ID NO:2 that after truncation or deletion, substitution and other structural modification will retain the same structure as SEQ ID NO:2 is unpredictable. And, the compound that is produced by screening an interaction of substances with the variant polypeptide is unpredictable as well.

The current application discloses only the cDNA-encode polypeptide SEQ ID NO: 2. In page 15, the specification describes a computer-assisted protein folding simulation for structurally selecting and evaluating the fragments (*i.e.*, polypeptide variants). One of ordinary skill in the art cannot envision all the contemplated amino acid sequence possibilities recited in the instant claims. Consequently, conception in the above cases cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. The current disclosure only provide working examples for identifying and charactering the proteins that interact with the

full-length SEQ ID NO:2 protein TTRAP, which are TRF-RII, the TRAF3 and TRAF5 proteins, and CD40 cytoplasmic domain (see examples 5-7). However, the current application provide no working example(s) nor sufficient guidance as to what is a correlation between the disclosed TTRAP protein and treating CD40 related diseases, *e.g.*, atherosclerosis arthritis, multiple sclerosis, systemic lupus erythematosis, graft rejection and the like [see page 12, lines 1-3], and how pharmaceutical composition comprising formulation of the TTRAP interacting compound are useful for treating the CD40 related diseases mentioned above. Likewise, all the variant polypeptides (70% to leas than 100% and any fragment thereof) are not enabling for the claimed pharmaceutical composition as well.

Because the current disclosure does not describe an actual reduction to practice of the claimed invention, the applicants are not in position of all variant polypeptides of 70% to less than 100% and their pharmaceutical use for treating a CD40 disease state.

(2) The scope of the claims:

The specification sets forth that the compound (set forth in claim 20) is any chemical (including inorganic and organic compounds) and biological (including peptides, peptido-mimetics, proteins, antibodies, carbohydrates or nucleic acids) [see page 16, lines 8-10]. The specification provides no working examples and guidance as to how to use the TTRAP protein or a fragment thereof for detecting and characterizing a compound capable of interacting with the TTRAP protein at least. In addition, the term "interacting" in the claim encompasses positive or/and negative regulation of the TTRAP protein, whereas the specification is silent as to this regard. Thus, in this point of view, the scope of claims is also broader than the enabling disclosure.

In addition, claim 20 sets forth screening the compound that interacts with a fragment of full-length TTRAP protein, which has not been yet taught or described in the specification. Therefore, it renders the scope of claims being out of the scope of the enablement.

(3) The state of the prior art:

The general knowledge and level of skilled in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe common attribute and characteristics that identify any biological active fragments for its use, one of skilled artisan is require performing undue experimentation in order to screen, identify and isolate appropriate truncated full-length TTRAP polypeptides.

It has been known that tumor necrosis factor receptor-associated factors (TRAFs) associate with the CD40 cytoplasmic domain and initiate signaling after CD40 receptor multimerization by its ligand. The current invention is directed to a CD40-interacting and TRAF-interacting protein, *i.e.*, TTRAP protein (SEQ ID NO:2). Galibert. L. *et al.* (*J. Biol. Chem.* (1998) 273, 34120-34127) show that a truncation mutant of a TRAF protein impairs its cellular signaling properties, suggesting that mutational alteration in CD40 interacting protein has a dramatic impact on the biological ability of the protein.

The disclosure fails to describe the consequence of the variants, *i.e.*, truncation or deletion mutants and their interacting compound(s) as a component of the pharmaceutical composition. Thus, the specification needs to provide sufficient guidance to support enabling.

(4) The unpredictability of the art:

Because 70% to less than 100% homology to full-length sequence of TTRAP and truncation mutants (*i.e.*, fragments of the full-length TTRAP) are highly variant, and use of them

for detecting a compound being able to *negatively* or *positively* regulate TTRAP or/and the TTRAP truncation mutants and thereby to modulate CD40 signaling activity thereof are highly variant. TTRAP protein that is the subject matter of this invention acts as a modulator for TNF receptor and/or CD40. Since the claimed TTRAP variants are unpredictable in structure and function (*e.g.*, a negative regulator or a positive regulator), the ability of the variants to couple CD40 or/and TNF receptor is not invariable, which would render the current disclosure unpredictable.

(5) The quantity of experimentation necessary:

In the absence of working examples with regard to the numerous variant sequences, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the current application are directed to numerous variants of polypeptide fragments, whereas the current disclosure provides no working examples with respect to structure and function of these variants nor how to *a priori* determine which one(s) would or would not have been functional or not. Of them, some thus would have unpredictable cell-signaling activities. Therefore, in this regard, the quantity of experimentation would be undue. One skilled in the art would be required to carry out an undue experimentation for screening and making variants which have desirable biological or therapeutic activities.

(6) The relative skill of those in the art:

The general knowledge and level of skill in the art do not supplement the omitted description with respect to a massive number of variant sequences of polypeptide. In view of the preceding factors (1-5), the level of skill in this art is high and requires at least a cell biologist or physician with several years of experience in biochemistry, molecular biology, immunology as

well as knowledge in mutagenesis and pharmacology; yet, even with a level of skill in the art as those mentioned in precedence, predictability of the results is still highly variable.

As exemplified above, not only the truncation fragments are unpredictable as to their biological activities of interacting with TNF family receptor, TRAF proteins and CD40 receptor and interacting with the compound(s) that binds full-length TRRAP, but also are unpredictable the compound(s) positively or negatively regulating the TTRAP signaling activity *per se*. An unduly level of skill is needed for the skilled artisan to resolve the above mentioned unpredictability issues in order to enable produce a pharmaceutical composition comprising the identified compound(s).

In consideration of each of factors stated above, absent factual data to the contrary, the amount and level of experimentation needed is undue.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is (703) 306-3483. The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 703 308-2923. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

Samuel Wei Liu

December 10, 2002

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